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Codon usage patterns in *Escherichia coli*, *Bacillus subtilis*, *Saccharomyces cerevisiae*, *Schizosaccharomyces pombe*, *Drosophila melanogaster* and *Homo sapiens*; a review of the considerable within-species diversity

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ABSTRACT

The genetic code is degenerate, but alternative synonymous codons are generally not used with equal frequency. Since the pioneering work of Grantham's group (1,2) it has been apparent that genes from one species often share similarities in codon frequency; under the "genome hypothesis" (1,2) there is a species-specific pattern to codon usage.

However, it has become clear that in most species there are also considerable differences among genes (3-7). Multivariate analyses have revealed that in each species so far examined there is a single major trend in codon usage among genes, usually from highly biased to more nearly even usage of synonymous codons. Thus, to represent the codon usage pattern of an organism it is not sufficient to sum over all genes (8), as this conceals the underlying heterogeneity. Rather, it is necessary to describe the trend among genes seen in that species. We illustrate these trends for six species where codon usage has been examined in detail, by presenting the pooled codon usage for the 10% of genes at either end of the major trend (Table 1).

Closely-related organisms have similar patterns of codon usage, and so the six species in Table 1 are representative of wider groups. For example, with respect to codon usage, *Salmonella typhimurium* closely resembles *E.coli* (9), while all mammalian species so far examined (principally mouse, rat and cow) largely resemble humans (4,8).

CAUSES OF WITHIN-SPECIES DIVERSITY

Biased codon usage may result from a combination of several factors, viz. biases in the pattern of mutation, (translational) selection among synonymous codons, or selection against particular structures in DNA. Within-species heterogeneity in codon usage has been most clearly elucidated in *E.coli*; the major trend is from a strong bias towards a particular subset of codons in highly expressed genes to more even codon usage in lowly expressed genes (3,4,7). The heavily favoured codons in highly expressed *E.coli* genes are those best recognised by the most abundant tRNA species (3,4), and it seems clear that selection mediated by the translation process can occur among alternative synonymous codons (10,11). In contrast, most of the deviation from equal synonym use in the lowly expressed genes is likely to reflect nonrandom patterns of mutation (7,12). Then the pattern of bias in a particular gene reflects a mutation-selection balance at a point determined by the strength of translational selection on that gene (7,9,12).

Similar observations have been made for *S.cerevisiae* (4,5,12,13). In *B.subtilis* (14) and *S.pombe* (15) there are similar trends among genes, but there is less information about tRNA abundances. The pattern of codon

Table 1. Codon usage diversity within six species.

		<u>E.coli</u>		<u>B.subtilis</u>		<u>S.cerevisiae</u>		<u>S.pombe</u>		<u>Drosophila</u>		<u>Human</u>	
		high	low	high	low	high	low	high	low	high	low	G+C	A+T
Phe	UUU	0.34	1.33	0.70	1.48	0.19	1.38	0.44	1.28	0.12	0.86	0.27	1.20
	UUC	1.66	0.67	1.30	0.52	1.81	0.62	1.56	0.72	1.88	1.14	1.73	0.80
Leu	UUA	0.06	1.24	2.71	0.66	0.49	1.49	0.28	1.79	0.03	0.62	0.05	0.99
	UUG	0.07	0.87	0.00	1.03	5.34	1.48	2.16	0.80	0.69	1.05	0.31	1.01
Leu	CUU	0.13	0.72	2.13	1.24	0.02	0.73	2.44	1.55	0.25	0.80	0.20	1.26
	CUC	0.17	0.65	0.00	0.93	0.00	0.51	1.13	0.31	0.72	0.90	1.42	0.80
	CUA	0.04	0.31	1.16	0.34	0.15	0.95	0.00	0.87	0.06	0.60	0.15	0.57
	CUG	5.54	2.20	0.00	1.80	0.02	0.84	0.00	0.68	4.25	2.04	3.88	1.38
Ile	AUU	0.48	1.38	0.91	1.38	1.26	1.29	1.53	1.77	0.74	1.27	0.45	1.60
	AUC	2.51	1.12	1.96	1.14	1.74	0.66	1.47	0.59	2.26	0.95	2.43	0.76
	AUA	0.01	0.50	0.13	0.48	0.00	1.05	0.00	0.64	0.00	0.78	0.12	0.64
Met	AUG	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Val	GUU	2.41	1.09	1.88	0.83	2.07	1.13	1.61	2.04	0.56	0.74	0.09	1.32
	GUC	0.08	0.99	0.25	1.49	1.91	0.76	2.39	0.65	1.59	0.93	1.03	0.69
	GUA	1.12	0.63	1.38	0.76	0.00	1.18	0.00	1.06	0.06	0.53	0.11	0.80
	GUG	0.40	1.29	0.50	0.92	0.02	0.93	0.00	0.24	1.79	1.80	2.78	1.19
Ser	UCU	2.81	0.78	3.45	0.77	3.26	1.56	3.14	1.33	0.87	0.55	0.45	1.63
	UCC	2.07	0.60	0.00	0.81	2.42	0.81	2.57	0.52	2.74	1.41	2.09	0.80
	UCA	0.06	0.95	1.50	1.29	0.08	1.30	0.00	1.56	0.04	0.84	0.26	1.23
	UCG	0.00	1.04	0.00	0.94	0.02	0.66	0.00	0.67	1.17	1.30	0.68	0.13
Pro	CCU	0.15	0.75	2.29	0.99	0.21	1.17	2.00	1.21	0.42	0.43	0.58	1.50
	CCC	0.02	0.68	0.00	0.27	0.02	0.75	2.00	0.83	2.73	1.02	2.02	0.83
	CCA	0.42	1.03	1.14	1.08	3.77	1.38	0.00	1.51	0.62	1.04	0.36	1.57
	CCG	3.41	1.54	0.57	1.66	0.00	0.70	0.00	0.45	0.23	1.51	1.04	0.10
Thr	ACU	1.87	0.76	2.21	0.39	1.83	1.23	1.89	1.52	0.65	0.70	0.36	1.45
	ACC	1.91	1.29	0.00	0.98	2.15	0.78	2.11	1.04	3.04	1.58	2.37	0.92
	ACA	0.10	0.68	1.38	1.64	0.00	1.38	0.00	1.04	0.10	0.77	0.36	1.45
	ACG	0.12	1.28	0.41	0.98	0.01	0.60	0.00	0.40	0.21	0.95	0.92	0.18
Ala	GCU	2.02	0.61	2.94	0.78	3.09	1.07	2.30	1.79	0.95	0.91	0.45	1.59
	GCC	0.18	1.18	0.08	1.14	0.89	0.76	1.49	0.50	2.82	1.93	2.38	0.92
	GCA	1.09	0.79	0.60	1.19	0.03	1.49	0.21	1.14	0.09	0.59	0.36	1.38
	GCG	0.71	1.42	0.38	0.89	0.00	0.68	0.00	0.57	0.14	0.57	0.82	0.11

Relative Synonymous Codon Usage (RSCU; Ref.5) values are presented for two groups of genes from each of six species: Escherichia coli, Bacillus subtilis, Saccharomyces cerevisiae, Schizosaccharomyces pombe, Drosophila melanogaster and Homo sapiens.

(An RSCU value is the observed number of codons divided by the number expected if all codons for that amino acid were used equally.)

Table 1 (cont.)

		<u>E.coli</u>		<u>B.subtilis</u>		<u>S.cerevisiae</u>		<u>S.pombe</u>		<u>Drosophila</u>		<u>Human</u>		
		high	low	high	low	high	low	high	low	high	low	G+C	A+T	
Tyr	UAU	0.38	1.28	0.50	1.29	0.06	1.13	0.48	1.24	0.23	0.96	0.34	1.17	UAU
	UAC	1.63	0.72	1.50	0.71	1.94	0.87	1.52	0.76	1.77	1.04	1.66	0.83	UAC
	UAA	--	--	--	--	--	--	--	--	--	--	--	--	UAA
	UAG	--	--	--	--	--	--	--	--	--	--	--	--	UAG
His	CAU	0.45	1.21	2.00	1.28	0.32	1.16	0.56	1.44	0.29	0.86	0.30	1.28	CAU
	CAC	1.55	0.79	0.00	0.72	1.68	0.84	1.44	0.56	1.71	1.14	1.70	0.72	CAC
Gln	CAA	0.12	0.76	1.71	0.88	1.98	1.10	1.85	1.67	0.03	0.88	0.21	0.98	CAA
	CAG	1.88	1.24	0.29	1.13	0.02	0.90	0.15	0.33	1.97	1.12	1.79	1.02	CAG
Asn	AAU	0.02	1.12	0.47	1.21	0.06	1.28	0.30	1.41	0.13	1.13	0.33	1.20	AAU
	AAC	1.98	0.88	1.53	0.79	1.94	0.72	1.70	0.59	1.87	0.87	1.67	0.80	AAC
Lys	AAA	1.63	1.50	1.83	1.47	0.16	1.24	0.10	1.27	0.06	0.81	0.34	1.17	AAA
	AAG	0.37	0.50	0.17	0.53	1.84	0.76	1.90	0.73	1.94	1.19	1.66	0.83	AAG
Asp	GAU	0.51	1.43	0.53	1.16	0.70	1.38	0.78	1.56	0.90	1.10	0.36	1.29	GAU
	GAC	1.49	0.57	1.47	0.84	1.30	0.62	1.22	0.44	1.10	0.90	1.64	0.71	GAC
Glu	GAA	1.64	1.28	1.40	1.27	1.98	1.29	0.69	1.20	0.19	0.73	0.26	1.33	GAA
	GAG	0.36	0.72	0.60	0.73	0.02	0.71	1.31	0.80	1.81	1.27	1.74	0.67	GAG
Cys	UGU	0.60	0.94	0.00	0.94	1.80	1.10	0.14	1.56	0.07	0.71	0.42	1.09	UGU
	UGC	1.40	1.06	2.00	1.06	0.20	0.90	1.86	0.44	1.93	1.29	1.58	0.91	UGC
ter	UGA	--	--	--	--	--	--	--	--	--	--	--	--	UGA
Trp	UGG	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	UGG
Arg	CGU	4.47	1.71	3.11	0.54	0.63	0.64	5.17	1.89	2.65	0.69	0.38	0.64	CGU
	CGC	1.53	2.41	1.78	1.21	0.00	0.39	0.83	0.26	3.07	1.55	2.72	0.36	CGC
	CGA	0.00	0.52	0.00	0.74	0.00	0.65	0.00	0.86	0.07	1.12	0.31	0.81	CGA
	CGG	0.00	0.80	0.00	0.81	0.00	0.34	0.00	0.43	0.00	1.12	1.53	0.51	CGG
Ser	AGU	0.13	1.01	0.45	0.56	0.06	0.97	0.14	1.48	0.04	0.89	0.31	1.26	AGU
	AGC	0.93	1.62	0.60	1.63	0.16	0.70	0.14	0.44	1.13	1.01	2.22	0.94	AGC
Arg	AGA	0.00	0.37	1.11	2.02	5.37	2.51	0.00	1.71	0.00	0.56	0.22	2.40	AGA
	AGG	0.00	0.19	0.00	0.67	0.00	1.47	0.00	0.86	0.21	0.95	0.84	1.28	AGG
Gly	GGU	2.27	1.29	1.38	0.54	3.92	1.32	3.36	1.87	1.34	0.91	0.34	0.84	GGU
	GGC	1.68	1.31	0.97	1.30	0.06	0.92	0.59	0.27	1.66	1.65	2.32	0.76	GGC
	GGA	0.00	0.64	1.66	1.24	0.00	1.22	0.05	1.60	0.99	0.98	0.29	1.79	GGA
	GGG	0.04	0.76	0.00	0.92	0.02	0.55	0.00	0.27	0.00	0.46	1.05	0.61	GGG

For each species, genes have been ranked according to their position along the major intraspecific trend in codon bias (see text). The highest 10% and the lowest 10% of genes have been drawn from: 165 E.coli genes (7), 76 B.subtilis genes (8,14), 154 S.cerevisiae genes (5,8), 40 S.pombe genes (15), 84 D.melanogaster genes (16) and 290 human genes (8). The sample size for S.pombe is rather small, but the codon frequencies appear to be reliable (15). Full gene listings are available from the authors.

frequencies in lowly expressed genes from *B.subtilis* is most strongly indicative of mutational bias (14).

Recently, we have reported evidence of selection among synonymous codons in the multicellular organism *D.melanogaster* (16). In contrast, among human genes the major variation is in G+C content associated with the local base composition around the gene (6). This variation has not been attributed to translational selection, and is most easily explained in terms of variation in mutation biases among chromosomal regions.

CODON BIAS RANKINGS

For *E.coli*, *B.subtilis*, *S.cerevisiae* and *S.pombe* codon bias in a gene is measured by the Codon Adaptation Index (CAI). A species-specific reference set of very highly expressed genes is used to assess the relative fitness of each synonymous codon, and the CAI for a gene is then calculated as the geometric mean of the fitness values for each codon in that gene. (For a full description, see Ref.17.)

Since the biological basis of codon frequencies in *Drosophila* is not yet so firmly established (for example, there may be more than one optimal set of codons, depending on the tissue of gene expression) we have simply estimated codon bias as the deviation from equal synonym use, by a "chi-square" scaled by gene length (16); this index is very highly correlated with the major trend among genes. Finally, human genes are ranked by G+C content at silent positions, since this is the major source of variation among genes (4,6).

FORTRAN 77 programs to calculate these indices are available (on IBM-type floppy disks) from the authors on request.

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REFERENCES

1. Grantham, R., Gautier, C., Gouy, M., Mercier, R. and Pave, A. (1980) Nucleic Acids Res. 8, r49-r62.
2. Grantham, R., Gautier, C., Gouy, M., Jacobzone, M. and Mercier, R. (1981) Nucleic Acids Res. 9, r43-r74.
3. Gouy, M. and Gautier, C. (1982) Nucleic Acids Res. 10, 7055-7074.
4. Ikemura, T. (1985) Mol. Biol. Evol. 2, 13-34.
5. Sharp, P.M., Tuohy, T.M.F. and Mosurski, K.R. (1986) Nucleic Acids Res. 14, 5125-5143.
6. Aota, S. and Ikemura, T. (1986) Nucleic Acids Res. 14, 6345-6355.
7. Sharp, P.M. and Li, W-H. (1986) Nucleic Acids Res. 14, 7737-7749.
8. Aota, S., Gojobori, T., Ishibashi, F., Maruyama, T. and Ikemura, T. (1988) Nucleic Acids Res. 16, r315-r402.
9. Ikemura, T. (1985) in Molecular Evolution and Population Genetics, Aoki, K. and Ohta, T. Eds., pp. 385-406, Springer-Verlag, Berlin.

10. de Boer, H. and Kastelein, R.A. (1986) in From gene to protein; steps dictating the maximal level of gene expression, Reznikoff, W.S. and Gold, L. Eds., pp. 225-283, Butterworths, Mass.
11. Kurland, C.G. (1987) Trends Biochem. Sci. 12, 126-128.
12. Bulmer, M. (1988) J. Evol. Biol. 1, 15-26.
13. Bennetzen, J.L. and Hall, B.D. (1982) J. Biol. Chem. 257, 3026-3031.
14. Shields, D.C. and Sharp, P.M. (1987) Nucleic Acids Res. 15, 8023-8040.
15. Sharp, P.M. and Wright, F. (1988) in preparation
16. Shields, D.C., Sharp, P.M., Higgins, D.G. and Wright, F. (1988) Mol. Biol. Evol. 5 (in press)
17. Sharp, P.M. and Li, W-H. (1987) Nucleic Acids Res. 15, 1281-1295.